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THERMODYNAMICS OF METALLOPROTEIN ELECTRON TRANSFER REACTIONS

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Abstract - Thin-layer spectroelectrochemical methods have been used to determine the formal reduction potentials of several electron transfer metalloproteins in the temperature range 5-40°C (5-26°C for plastocyanin). Measurements were made using OTTLE cells in a nonisothermal configuration. Electron transfer reaction entropies ($\Delta S^\circ_{rc} = S^\circ_{red} - S^\circ_{ox}$) at 25°C (pH 7, μ = 0.1 M) derived from these measurements are as follows: cytochrome *c* (horse heart), -14.9 ± 1.2; cytochrome c_2 (*Rhodospirillum rubrum*), -9.6 ± 1.2; cytochrome c_{551} (*Pseudomonas aeruginosa*), -16.2 ± 1.2; HiPIP (*Chromatium vinosum*), -10.0 ± 1.2; azurin (*Pseudomonas aeruginosa*), -16.1 ± 1.2; stellacyanin (*Rhus vernicifera*), -4.2 ± 1.2; plastocyanin (*Phaseolus vulgaris*), -2.4 ± 1.2 eu. In all cases the ΔH° values are negative. The fact that the ΔS°_{rc} values are more negative than inorganic complexes with low inner sphere electron transfer barriers is discussed in terms of changes in protein-solvent interactions that could accompany reduction. Either increased solvent ordering in the protein interior or a more compact protein structure in which solvent is excluded could account for the observed loss in entropy in the reduced solution state.

INTRODUCTION

Our continued interest in understanding the electron transfer mechanisms employed by biological systems has led us to investigate the thermodynamics of metalloprotein redox reactions. The thermodynamics of the electron transfer reactions could provide information relating to solvation and protein conformational changes between the oxidized and reduced species (1). This information should complement the large body of kinetic data that is available and provide a more complete picture of biological electron transfer in general.

We have focused mainly on thin-layer spectroelectrochemical methods employing semitransparent minigrid electrodes (2-4), since ample evidence now exists (5-12) that these techniques are well suited for studying biological systems. Heterogeneous electron transfer between the electrode surface and metalloprotein redox couples is effectively catalyzed (13-16) by the addition of so-called "mediator-titrants". The progress of the redox reaction is usually followed (17) by spectroscopy (*i.e.*, uv-visible, IR, internal reflectance). Thin-layer spectroelectrochemistry (2-4) is capable of determining formal reduction potentials (E°'s), the number of electrons (n) involved in the reduction process, and the absorption spectra of the oxidized and reduced forms of the redox couples.

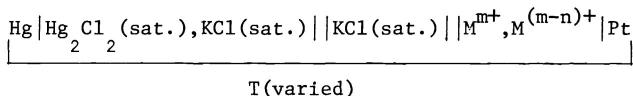
METHODS

Our efforts have focused on improving the range and sensitivity of the OTTLE technique, in addition to developing cells suitable for anaerobic (6,12,13) and variable temperature (18) studies. Gold electroformed mesh (minigrid, 60% transmittance) is used as the working electrode for the metalloprotein studies. Cell thicknesses are varied from 0.1 to 0.4 mm, with two opposing minigrids employed in the thicker cells. Thin-layer cell volumes vary from about 40 to 100 µL with an additional solution dead volume of 0.7 mL. Lucite (methyl methacrylate) and Kel-F (teflon) are employed as cell body materials and high quality quartz (transparency to 170 nm) is used for the cell windows. A fully detailed description of our OTTLE cell designs and all the accompanying technical apparatus will be given elsewhere (19).

The formal reduction potential, E°, for a redox couple is determined by sequentially applying a series of potentials, E(applied), across the thin-layer cell. Each potential is maintained until electrolysis ceases so that the equilibrium value of the ratio of the concentrations of reduced to oxidized forms, [R]/[O], is established as defined by the Nernst equation.

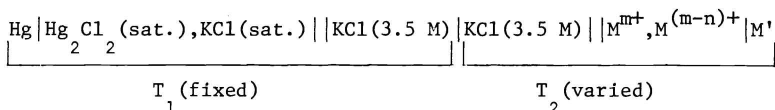
Complete electrolysis occurs rapidly due to the short diffusional path length created by the thin solution layer. The redox couple is incrementally converted from one oxidation state to the other by the series of applied potentials, for which each corresponding value of [R]/[O] is determined from the spectra. Formal reduction potentials and n values are determined from plots of E(applied) versus log[R]/[O].

The thermodynamics of the redox reactions of several transition metal complexes in aqueous solution have been examined in some detail (20-30). Measurements of the temperature coefficient of the e.m.f. of electrochemical cells of the type (25)



were usually employed in the earlier studies (M^{m+} and $M^{(m-n)+}$ refer to the oxidized and reduced halves of the redox couple of interest). Formal reduction potentials at each temperature were determined potentiometrically using solutions containing equimolar concentrations of the oxidized and reduced halves of the redox couple. Such cell arrangements contain enthalpy and entropy contributions from the reference electrode half-cell in the temperature coefficient of the cell e.m.f. and are referred to as "isothermal" cells. An inherent difficulty with this procedure lies in the long time needed for most common reference electrodes to reach temperature equilibrium (days may be required in certain instances (25)).

It has recently been demonstrated (28) that a cell arrangement of the type

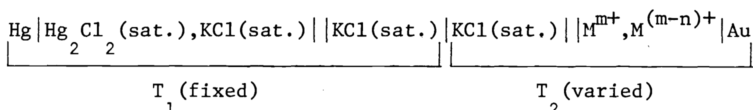


is well-suited for determining the thermodynamics of redox reactions in aqueous solution if certain thermal junction potentials are either negligible or are constant and can be determined (M' represents the appropriate working electrode, e.g., Hg, Pt, etc.). Under favorable circumstances the partial molal ionic entropy difference between the reduced and oxidized halves of the redox couple of interest (i.e., the "reaction entropy", ΔS°_{rc}) is directly proportional to the temperature coefficient of the nonisothermal cell (28):

$$\Delta S^\circ_{rc} = S^\circ_{red} - S^\circ_{ox} = F(dE^\circ/dT) \tag{1}$$

where F is the Faraday.

We have employed the nonisothermal configuration in the construction of our OTTLE cells for variable temperature studies. The following arrangement is utilized



where Au represents the gold minigrid electrode. Our nonisothermal salt bridge consists of a 5 mm x 25 cm glass tube filled with saturated KCl solution. The bottom end is closed with a porous frit and a micro saturated calomel reference electrode resides at the top. The temperature of the OTTLE cell is varied using a specially constructed variable temperature cell holder and cell temperatures are directly measured with a precision micro-thermocouple (plus digital thermometer, ±0.1°C) situated in the protein solution in close proximity to the thin layer cavity. The reference electrode and part of the nonisothermal salt bridge are maintained at the ambient room temperature. Reduction potentials at different temperatures were determined using the spectropotentiostatic procedure described above. The Nernst plot data were analyzed using a linear least squares fit to the Nernst equation and reduction potentials were retained only if the Nernst slopes (2.303RT/nF) were within ±3 mV of the theoretical slopes at the given temperature and the linear correlation coefficients were $\geq$0.999.

NONISOTHERMAL CELL BEHAVIOR OF THE VARIABLE TEMPERATURE OTTLE CELLS

All of the OTTLE cells employed were initially characterized by performing spectropotentiostatic experiments on known systems such as horse heart cytochrome c and $Fe(CN)_6^{3-/4-}$ and by recording current-potential curves at low scan rates (e.g., 2 mV/s) on systems such as $Fe(CN)_6^{3-/4-}$ and $Co(phen)_3^{3+/2+}$.

We have taken an empirical approach in the characterization of our nonisothermal electrochemical cell arrangement. The thermodynamics of the metal 3+/2+ oxidation state change in

the tris-o-phenanthroline complexes of iron and cobalt were determined using our apparatus. The results were compared with published values for these same systems using cyclic voltammetry in a nonisothermal configuration and using potentiometry in an isothermal configuration.

For all the systems studied (including the metalloproteins), at least 10 reduction potentials were measured in the temperature ranges investigated. The temperature coefficient of the reduction potential, $dE°/dT$, was determined as the slope of a linear least squares fit to the $E°$ *versus* temperature data. Because we were testing a nonisothermal cell arrangement, reaction entropies ($\Delta S°_{rc} = S°_{red} - S°_{ox}$ values) were calculated directly from equation 1. Entropies for the complete cell reaction adjusted to the NHE scale, $\Delta S°$, were determined from the relation (22)

$$\Delta S° = (S°_{red} + S°_{H^+}) - (S°_{ox} + 1/2 \cdot S°_{H_2}) = (S°_{red} - S°_{ox}) - 15.6 \text{ eu} \quad (2)$$

taking $S°_{H_2}$ = 31.2 eu (32) and adhering to the arbitrary convention (1,20-22,25-27,33-37) that $S°_{H^+}$ be taken as zero. Standard free energy changes for the cell reaction were calculated from the $E°$ (V *vs.* NHE) values at 25.0°C and the standard enthalpy changes, $\Delta H°$'s, were determined from the corresponding $\Delta G°$'s and $\Delta S°$'s.

It should be pointed out that $\Delta S°_{rc}$ ($=S°_{red} - S°_{ox}$) values determined from nonisothermal cell measurements are absolute quantities independent of any convention. Because some precedent exists (25,27,30,31) for an "absolute" entropy scale based on $S°_{H^+}$ = -5.5 eu (31,38), caution must be exercised in converting $\Delta S°_{rc}$ to $\Delta S°$ values and *vice versa*. In spite of the fact that some recent publications (28-30,39), including our initial report (9), have employed the absolute scale for interconverting $\Delta S°$ and $\Delta S°_{rc}$ values, we have decided to adhere to the arbitrary or "practical" (27) entropy scale (*cf.*, equation 2) in the present and in all future work. This decision is based on the fact that the vast majority of the current literature (1,20-22,25-27,33-37) employs this convention. Thus, direct comparison of metalloprotein $\Delta S°$ and $\Delta S°_{rc}$ ($=S°_{red} - S°_{ox}$) values obtained from different laboratories will be facilitated by adopting the most consistent convention for reporting entropy changes (33-37, *cf.* also Table 3) accompanying metalloprotein electron transfer reactions.

TABLE 1. Values of $\Delta S°$ and $\Delta S°_{rc}$ ($=S°_{red} - S°_{ox}$) for the metal 3+/2+ oxidation state change in the tris-o-phenanthroline complexes of iron and cobalt.

Couple	$\Delta S°$ (eu)	$S°_{red} - S°_{ox}$ (eu)	Electrolyte	Method	Ref.
$Fe(phen)_3^{3+/2+}$	-20.8 ± 2	-5.2 ± 2	4.5×10^{-3} M HNO_3 μ = 0.1 M ($NaNO_3$)	isothermal potentiometric Pt electrode	(22)
	-12.6 ± 2	3 ± 2	0.05 M KCl + 25 mM phen	nonisothermal C. V.[a] Pt electrode	(28)
	-20.6 ± 4	-5 ± 4[b]	4.5×10^{-3} M HNO_3 μ = 0.1 M ($NaNO_3$)	nonisothermal OTTLE Au electrode	(c)
$Co(phen)_3^{3+/2+}$	-3.6	12	μ = 0.01 M	isothermal potentiometric Pt electrode	(40)
	6.4 ± 4	22 ± 3	0.05 M KCl + 25 mM phen	nonisothermal C. V. Pt electrode	(28)
	2.7 ± 3	18 ± 3[d]	phosphate buffer μ = 0.1 M pH 7	nonisothermal OTTLE Au electrode	(c)

[a]Cyclic voltammetry.
[b]From E° *vs.* temperature data collected in the range 5-20°C.
[c]This work.
[d]From E° *vs.* temperature data collected in the range 5-28°C.

Table 1 summarizes the published $\Delta S°$ and $\Delta S°_{rc}$ values for the $Fe(phen)_3^{3+/2+}$ (22,28) and $Co(phen)_3^{3+/2+}$ (28,40) couples along with the results obtained in this work; the

corresponding reduction potentials, free energies, and enthalpies are given in Table 2. The enthalpies and entropies for the $Fe(phen)_3^{3+/2+}$ couple obtained from the nonisothermal OTTLE experiment agree surprisingly well with the published results for the isothermal potentiometric experiment at the same pH and ionic strength. Furthermore, the results for $Fe(phen)_3^{3+/2+}$ from nonisothermal cyclic voltammetry are also in satisfactory agreement considering the different electrolyte conditions under which the experiments were run. The enthalpies and entropies for $Co(phen)_3^{3+/2+}$ from the three different experimental methods are also consistent, indicating that the thermal junction potentials in our nonisothermal OTTLE cell arrangement are negligible given the precision of the reduction potentials being measured (±2 mV). We are therefore justified in using equation 1 for the calculation of reaction entropies for redox couples that are suitable for study with our nonisothermal OTTLE cell arrangement.

TABLE 2. Additional thermodynamic parameters for the metal 3+/2+ oxidation state change in the tris-o-phenanthroline complexes of iron and cobalt. Supporting electrolytes are the same as those given in Table 1.

Couple	E° (25°C) (V vs. NHE)	ΔG° (kcal/mol)	ΔH° (kcal/mol)	Method	Ref.
$Fe(phen)_3^{3+/2+}$	1.099	-26.5 ± 0.1	-32.7 ± 0.5	isothermal potentiometric Pt electrode	(22)
	1.114	-25.7	-29.3	nonisothermal C. V. Pt electrode	(28)
	1.072[a] (±0.004)	-24.7 ± 0.1	-30.8 ± 1.3	nonisothermal OTTLE Au electrode	(b)
$Co(phen)_3^{3+/2+}$	0.399	-9.2	-10.3	isothermal potentiometric Pt electrode	(40)
	0.387	-8.9	-9.2	nonisothermal C. V. Pt electrode	(28)
	0.377 (±0.002)	-8.7 ± 0.1	-9.5 ± 0.3	nonisothermal OTTLE Au electrode	(b)

[a]The value for E° at 25°C was extrapolated from the experimentally determined dE°/dT.
[b]This work.

RESULTS FOR METALLOPROTEIN REDOX REACTIONS

We have studied the thermodynamics of seven different metalloprotein electron transfer reactions using our nonisothermal OTTLE cells. Reduction potentials were measured (temperature range: 5-40°C) and the independence of the E°'s on the mediator-titrant employed was tested by measuring E° values with at least two different mediator-titrants for each metalloprotein. Table 3 lists published ΔS° and ΔS°_{rc} values for several metalloproteins along with those obtained in our studies. The corresponding reduction potentials, free energies, and enthalpies are given in Table 4. We have repeated our initial experiments (9) on azurin, stellacyanin, and plastocyanin using the more sophisticated apparatus described above and have arrived at the results listed in Tables 3 and 4. These values differ significantly from those given in reference (9). Because of apparent technical difficulties associated with the earlier measurements, we believe the present values are the more reliable.

All the metalloprotein electron transfer reactions exhibit negative ΔH° values, as expected for active sites in which the lower metal oxidation states (Fe(II) or Cu(I)) are stabilized by favorable metal-ligand electronic interactions (e.g., metal-ligand π back bonding). Information about changes in solvation and conformation of the proteins from oxidized to reduced states potentially could be extracted from the ΔS°_{rc} values, provided we had an appropriate framework on which to build an interpretation. Sutin, Weaver, and Yee have shown recently (39) that some correlations exist between ΔS°_{rc} values and k_{ex} (self-exchange rate constants) for inorganic complexes. Specifically, it appears that large positive values of ΔS°_{rc}, reflecting large solvent disordering in the reduced complexes, are associated with

TABLE 3. Metalloprotein $\Delta S°$ and $\Delta S°_{rc}$ values at 25°C and pH 7.

Metalloprotein	$\Delta S°$ (eu)	$S°_{red} - S°_{ox}$ (eu)	ionic strength (M)	Ref.
Cytochrome *c* (Horse heart)	-28 ± 5	-12 ± 5[a]	0.10	(33)
Cytochrome *c* (Horse heart)	-27.3	-11.7[b]	(c)	(34)
Cytochrome *c* (Horse heart)	-36.0 ± 1.5	-20 ± 1.5[d]	0.01	(1,35)
Cytochrome *c* (Horse heart)	-13.0	+3.0[d]	0.23	(1,35)
Cytochrome *c* (Horse heart)	-30.5 ± 1.2	-14.9 ± 1.2[e]	0.1	(f)
Cytochrome *c* (Baker's yeast iso-1-)	-37.0	-21[d]	0.01	(1,35)
Cytochrome *c* (*Candida krusei*)	-39.0	-23[d]	0.01	(1,35)
Cytochrome *c* (Tuna heart)	-39.0	-23[d]	0.01	(1,35)
Cytochrome *c* (Turkey heart)	-36.0	-20[d]	0.01	(1,35)
Cytochrome c_2 (*Rhodospirillum rubrum*)	-25.2 ± 1.2	-9.6 ± 1.2[e]	0.1	(f)
Cytochrome c_{551} (*Pseudomonas aeruginosa*)	-31.8 ± 1.2	-16.2 ± 1.2[e]	0.1	(f)
HiPIP (*Chromatium vinosum*)	-25.6 ± 1.2	-10.0 ± 1.2[e]	0.1	(f)
Azurin (*Pseudomonas aeruginosa*)	-31.7 ± 1.2	-16.1 ± 1.2[e]	0.1	(f)
Stellacyanin (*Rhus vernicifera*)	-19.8 ± 1.2	-4.2 ± 1.2[e]	0.1	(f)
Plastocyanin (*Phaseolus vulgaris*)	-18.0 ± 1.2	-2.4 ± 1.2[e,g]	0.1	(f)
Myoglobin	-38.0	-22	0.25	(36,37)
Hemoglobin	-38.0	-22	0.25	(36,37)

[a]From calorimetry on the oxidation of ferrocytochrome *c* by ferricyanide.

[b]From flow calorimetry on the oxidation of ferrocytochrome *c* by ferricyanide and on the reduction of ferricytochrome *c* by ascorbate.

[c]Total ionic strength was not reported in (34). However, the experiments at pH 7 were performed in 0.05 M phosphate buffer.

[d]From the temperature dependence of the equilibrium constant for the reaction ferrocytochrome *c* + ferricyanide = ferricytochrome *c* + ferrocyanide.

[e]From nonisothermal OTTLE experiments.

[f]This work.

[g]From E° *vs*. temperature data collected in the range 5-26°C.

small self-exchange rate constants (reflecting large inner sphere reorganization barriers). The most striking observation is that the $\Delta S°_{rc}$ values for the electron transfer metalloproteins are all negative; indeed, if we consider $\Delta S°_{rc}$ values obtained from our work, except for plastocyanin and stellacyanin they are 5 to 10 eu more negative than for the $Fe(phen)_3^{3+/2+}$ system, which from an inner sphere barrier point of view would appear to be an appropriate reference (41). Stellacyanin and plastocyanin exhibit the least negative $\Delta S°_{rc}$ values; and kinetic criteria suggest that the stellacyanin blue copper center is exposed in solution and likely undergoes adiabatic electron transfer with a variety of inorganic complexes (41).

TABLE 4. Additional thermodynamic parameters for the metalloprotein redox reactions at 25°C and pH 7. Ionic strengths and experimental methods are the same as those given in Table 3.

Metalloprotein	E° (V vs. NHE)	ΔG° (kcal/mol)	ΔH° (kcal/mol)	Ref.
Cytochrome c (Horse heart)	0.26	-6.0	-14.5 (± 1.5)	(33)
Cytochrome c (Horse heart)	0.259	-5.97	-14.1	(34)
Cytochrome c (Horse heart)	0.261 (±0.001)	-6.0 (±0.04)	-16.8 (± 0.5)	(1,35)
Cytochrome c (Horse heart)	0.260	-6.0	-10.0	(1,35)
Cytochrome c (Horse heart)	0.270 (±0.002)	-6.23 (±0.05)	-15.3 (± 0.4)	(a)
Cytochrome c (Baker's yeast iso-1-)	0.261 (±0.002)	-6.0 (±0.05)	-17.1	(1,35)
Cytochrome c (Candida krusei)	0.264 (±0.002)	-6.0 (±0.05)	-17.8	(1,35)
Cytochrome c (Tuna heart)	0.256 (±0.002)	-5.9 (±0.05)	-17.5	(1,35)
Cytochrome c (Turkey heart)	0.260 (±0.002)	-6.0 (±0.04)	-16.8	(1,35)
Cytochrome c_2 (Rhodospirillum rubrum)	0.324 (±0.002)	-7.47 (±0.05)	-15.0 (± 0.4)	(a)
Cytochrome c_{551} (Pseudomonas aeruginosa)	0.276 (±0.002)	-6.37 (±0.05)	-15.9 (± 0.4)	(a)
HiPIP (Chromatium vinosum)	0.352 (±0.002)	-8.12 (±0.05)	-15.8 (± 0.4)	(a)
Azurin (Pseudomonas aeruginosa)	0.308 (±0.002)	-7.10 (±0.05)	-16.6 (± 0.4)	(a)
Stellacyanin (Rhus vernicifera)	0.191 (±0.002)	-4.41 (±0.05)	-10.3 (± 0.4)	(a)
Plastocyanin (Phaseolus vulgaris)	0.360 (±0.002)	-8.30 (±0.05)	-13.7 (± 0.4)	(a,b)
Myoglobin	0.120	-2.8	-14.0	(36,37)
Hemoglobin	0.160	-3.7	-15.0	(36,37)

[a]This work.
[b]For E° vs. temperature data collected in the range 5-26°C.

The explanation of ΔS°_{rc} values more negative than $Fe(phen)_3^{3+/2+}$ is not clear. Two possibilities seem reasonable. One is that water molecules are highly ordered in the protein interiors in the reduced states of blue copper and heme c units, owing in part to charge neutralization of the redox centers in question (9). A second possibility is that the protein itself becomes more rigid in the reduced state. Internal solvent-protein interactions that tend to loosen the structure would not be as numerous in the reduced proteins, and the solvation of the protein would be due mainly to interactions at the surface of a more tightly-packed structure. It is not possible with the limited data now in hand to choose between these alternative explanations; indeed, it is entirely possible that some combination of protein conformation and solvation effects is responsible for the observed loss in entropy that accompanies electron transfer to the metalloprotein in solution.

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